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PATENT APPLICATION IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: Mader, et al. Group Art Unit: 1626

Serial No.: 10/535,002 Examiner: S. Young

Filing Date: November 13, 2003

US Nat'l Entry Date: May 12, 2005 Conf. No.: 9111

For: Antitumor Benzoylsulfonamides

Docket No.: X-16114

SUPPLEMENTAL PETITION TO THE TECHNOLOGY CENTER DIRECTOR UNDER 37 C.F.R. §1.144 FOR REVIEW AND MODIFICATION OF RESTRICTION REQUIREMENT

Technology Center Director P.O. Box 1450 Alexandria, VA 22313-1450 Sir:

The present application entered the U.S. national phase, through the PCT, under 35 U.S.C. §371. The present application was subjected to a restriction requirement purportedly under U.S.C. §121 and §372. On August 2, 2006, Applicants filed a petition to the Technology Center Director under 37 C.F.R. §1.144 for review and modification of the restriction requirement asserting that the restriction requirement was improper. In October 2006, the petition was granted as it relates to Group VI, but denied for Groups I-V. Applicants respectfully re-petition the Technology Center Director (Director) under 37 C.F.R. §1.144 to again review the requirement for restriction in the present application, to exercise the Director's supervisory authority, and to direct the Examiner to modify the improper restriction requirement.

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BACKGROUND OF THIS PETITION

The present application relates to novel compounds that are antitumor agents. The invention is claimed in Claims 1-5. Specifically, compounds presented in generic Claim 1 possess a core structure limited solely to 2,4-disubstituted benzoylsulfonamides. See Claim 1 below that is now pending for the present application:

1. A compound of Formula I:

$$Ar = \begin{bmatrix} O & O & R^1 \\ S & N & \\ O & H & \\ I & & \end{bmatrix}$$

where:

Aris

Ar is or a heterocycle selected from the group consisting of 2,3-dihydrobenzo[1,4]dioxin-6-yl, 2,3-dihydrobenzofur-5-yl, benzo[1,3]dioxol-5-yl, 1-(C₁-C₆ alkyl)indolin-6-yl, benzothien-2-yl, benzothien-5-yl, benzothien-6-yl, 5-(C₁-C₆ alkyl)benzothien-2-yl, 6-(C₁-C₆ alkyl)benzothien-2-yl, benzothiazol-6-yl, benzofur-2-yl, benzofur-6-yl, thieno[3,2-b]pyridin-2-yl, and 1-(C₁-C₆ alkyl)indol-2-yl;

A is phenyl, benzofuryl, cyclopentadienyl, cyclobutyl, or a cyclopentyl that is optionally substituted at one of the two carbons adjacent to the ring fusion of the cyclopentyl with an oxo moiety;

 R^1 and R^2 are either both halo, both trifluoromethyl, or one is halo and the other is $C_1\text{-}C_6$ alkyl; or

a pharmaceutically acceptable base addition salt thereof.

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DECISION

Applicants respectfully request that the Technology Center Director (Director) reconsider and modify the petition decision for Groups I through V (noting again that these groups are not all inclusive of Applicants' claimed subject matter), and direct the Examiner to modify the improper restriction requirement.

THE PRIOR PETITION DECISION

In the prior October 2006 decision on the petition, the Director found:

[T]here appears to be no indication that benzoylsulfonamides possess the antitumor activity claimed herein in the prior art which leads to the presumption that the activity is provided by the Ar substituents. In view of this conclusion Lack of Unity does exist between the different Ar groups attached to the benzoylsulfonamide structure.

THE APPLICABLE PROVISIONS

According to the unity of invention standard set forth in PCT Rule 13.2, unity of invention exists only when there is a technical relationship among the claimed inventions involving one or more of the same or corresponding "special technical features". The expression "special technical features" is defined in Rule 13.2 as meaning those technical features that define a contribution which each of the inventions considered as a whole, makes over the prior art.

Under (d) of PCT Gazette-Section IV, Annex B, Part 1, a copy of which is attached to the petition, there are three particular situations for which the method for determining unity of invention contained in Rule 13.2 is explained in greater detail. One of those situations is Markush practice.

The situation involving Markush practice wherein a single claim defines alternatives (chemical or non-chemical) is also governed by PCT Rule 13.2. In this situation, the requirement of a technical interrelationship and the same or corresponding special technical features as defined in PCT Rule 13.2 shall be considered to be met when the alternatives are of a similar nature.

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(i)When Markush grouping is for alternatives of chemical compounds, they shall be regarded as being of a similar nature where the following criteria are fulfilled:

- (A) All alternatives have a common property or activity; <u>and</u> (emphasis added)
- (B)(1) A common structure is present, i.e. a significant structural element is shared by all of the alternatives; **or** (emphasis added)
- (B)(2) In cases where the common structure cannot be the unifying criteria, all alternatives belong to a recognized class of chemical compounds in the art to which the invention pertains.
- (ii) In paragraph (f)(i)(B)(1), above, the words "significant structural element is shared by all of the alternatives" refer to cases where the compounds share a common chemical structure which occupies a large portion of their structures, or in case the compounds have in common only a small portion of their structures, the commonly shared structure constitutes a structurally distinctive portion in view of existing prior art. The structural element may be a single component or a combination of individual components linked together.
- (iii) In paragraph (f)(I)(B)(2, above, the words "recognized class of chemical compounds mean that there is an expectation from the knowledge in the art that members of the class will behave in the same way in the context of the claimed invention. In other words, each member could be substituted for the other, with the expectation that the same intended result would be achieved.
- (iv) The fact that the alternatives of a Markush grouping can be differently classified shall not, alone, be considered to be justification for a finding of a lack of unity of invention. PCT Gazette-Section IV, Annex B, Part 1 (f)

DISCUSSION OF THE APPLICABLE PROVISIONS AS THEY RELATE TO THE PETITION DECISION

The PCT guidelines for determining Unity of Invention for Markush Groups recited above, sets out a two-prong test to determine if the Markush grouping for alternatives of chemical compounds are of similar nature:

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(A) All <u>alternatives</u> have a common property or activity; <u>and</u> (emphasis added)

- (B)(1) A common structure is present, i.e. a significant structural element is shared by all of the alternatives; $\underline{\mathbf{or}}$ (emphasis added)
- (B)(2) In cases where the common structure cannot be the unifying criteria, all alternatives belong to a recognized class of chemical compounds in the art to which the invention pertains.

According to the Petition Decision, Applicants failed the first prong of the two-part test, "[a]ll alternatives have a common property or activity", due to a "presumption that the common property or activity asserted lies in the Ar substituent, not the benzolysulfonamide common structure".

However, the antecedent basis for the word "alternatives" is the phrase "alternatives of chemical compounds" found in (f)(i), not "common structure". Thus, in order for the first prong to be met, all alternatives of the chemical compounds must have a common property or activity. This point is re-emphasized by a slide presentation dated November 15, 2001, entitled "Lack of Unity in PCT Applications and 35 U.S.C. 371 Applications in Technology Center 1600", that can be found on the PTO website at www.uspto.gov/web/patents/biochempharm/documents/dixon.pps and a copy of which is attached for the Director's convenience. Slides 29 and 30 of this presentation illustrate an example of Markush practice using Example 18, an indole with four variable substituents (small substituents or rings). Although a lack of unity of invention was eventually found in this example due to the indole structure having been known (compounds having in common only a small portion of their structures), it is noteworthy that on slide 30 it states:

In this case, the indolyl moiety is the significant structural element that is shared by all of the alternatives. Since <u>all the claimed compounds are</u> <u>alleged to possess the same utility</u> [emphasis added], unity may be present."

It does not state that the indole is the common structure and thus, must also be solely responsible for the activity in order for unity of invention to exist. But instead, re-

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emphasizes that it is the claimed compounds that must possess the same utility in order for the first prong to be met.

In view of these points, the pending claims, Claims 1-5, meet the criteria of unity of invention under Rules 13.1/13.2. Applicants request that the restriction requirement be removed from the present application and that pending Claims 1-5 be examined in their entirety. Applicants assert that the restriction required by the Examiner of Groups I-V, does not satisfy the applicable standard and request that this petition be granted and the restriction removed.

SUMMARY

Applicants maintain that the Examiner has failed to apply the proper standard for restriction in the present application and based upon the above arguments, respectfully request the Director to reconsider Applicants' petition, modify the decision, and direct the Examiner to reunite and examine Groups I-V.

Respectfully submitted,

\Tina M. Tucker\

Tina M. Tucker Attorney for Applicants Registration No. 47,145 Phone: 317-277-3537

Eli Lilly and Company Patent Division/TMT P.O. Box 6288 Indianapolis, Indiana 46206-6288

Attachment:

"Lack of Unity in PCT Applications and 35 U.S.C. 371 Applications in Technology Center 1600", USPTO presentation slides dated November 15, 2001

PCT APPLICATIONS

AND 35 U.S.C. 371 APPLICATIONS

TECHNOLOGY CENTER 1600

Lacker Units Practice

PCT Chapter I & PCT Chapter II

§371 National Stage Filing

U.S. Restriction Practice

Continuation

Application filed under § 111(a) Priority claim under §119 or §120

Continuation-in-Part

Application filed under §111(a) Priority claim under §119 or §120

Continuation

Application filed under §111(a) Priority claim under §120

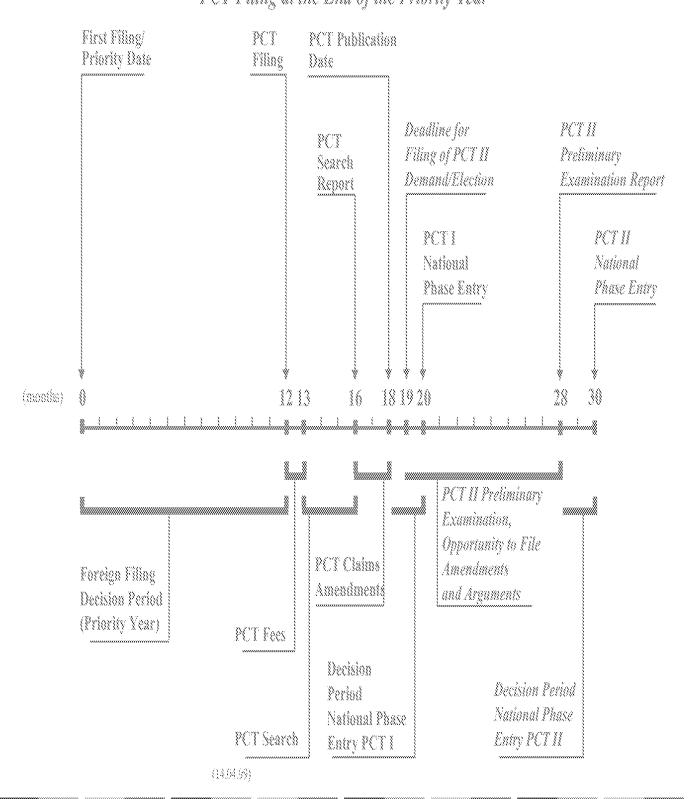
Continuation-in-Part

Application filed under §111(a)
Priority claim under §129

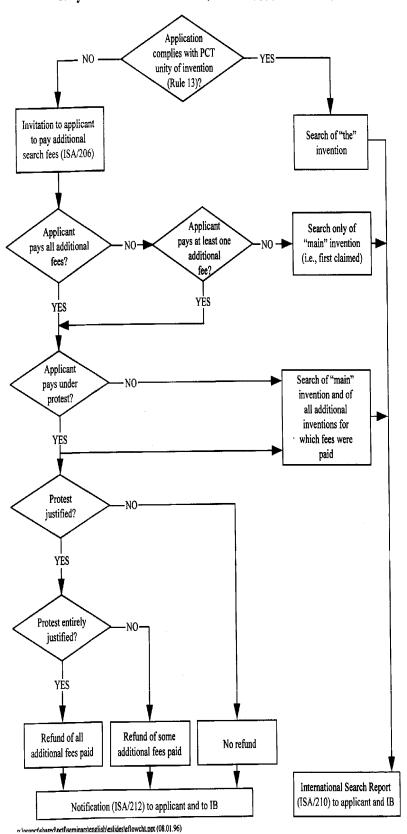
Divisional

Application filed under §111(a) Priority claim under §120

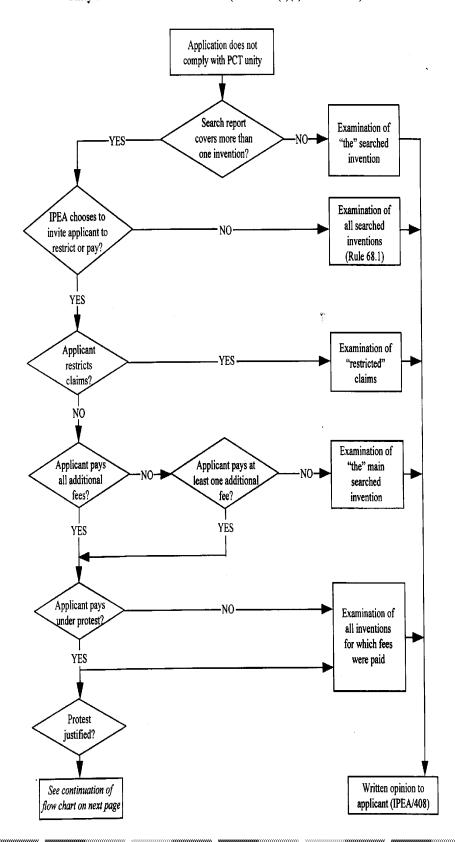
PCT TIMELINE A PCT Filing at the End of the Priority Year



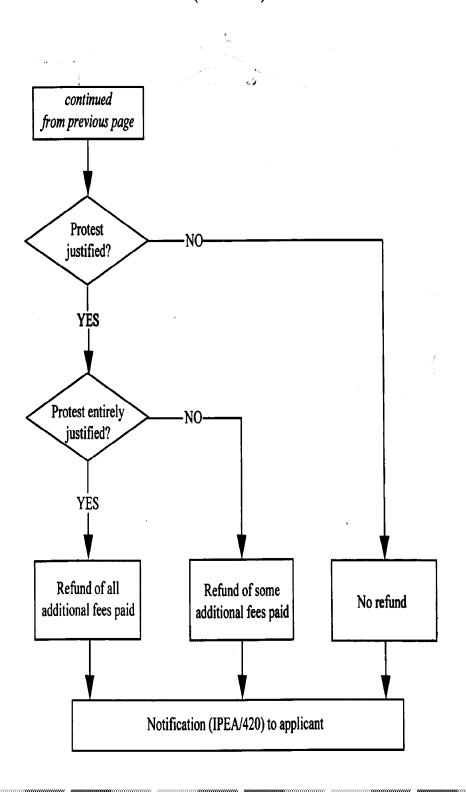
Unity of invention before the ISA (Article 17(3)(a) and Rule 40)



Unity of invention before the IPEA (Article 34(3)(a) and Rule 68)



Unity of invention before the IPEA (Article 34(3)(a) and Rule 68) (continued)



Lack of unity of invention before ISA

(Article 17(3) and Rule 40)

- 1. Where there are several inventions claimed, the first claimed invention ("main invention") is always searched; further inventions are searched only if additional search fees are paid.
- 2. The ISA will invite the applicant to pay additional search fees and will specify the reasons for the finding of lack of unity of invention.
- 3. Applicant can:

pay for the search of all additional inventions;

pay for the search of some additional (specified) inventions; or pay for the search of none of the additional inventions

Lack of unity of invention before ISA

(Article 17(3) and Rule 40) (con't)

3. Failure to pay additional fees does not affect the search of the first claimed invention.

However, the additional inventions will not be searched and, subsequently, the claims relating to unsearched inventions will not be examined by the IPEA.

4. Additional fees may be paid with or without protest.

Protest procedure under Chapter I (Rule 40.2)

- 1. If the applicant pays any or all additional fees under protest, the US/ISA carries out the search on the first claimed invention and the additional inventions paid for and, in parallel, reviews the protest of the invitation to pay additional fees.
- If, upon review, the ISA concludes that the invitation was not justified or not justified-in-part, all or some of the additional search fees will be refunded.
- If, upon review, the ISA concludes that the invitation was justified, the protest is denied. The applicant will be given detailed reasons for the denial.

A lack of unity requirement

- Can be made in Chapter II even if one had not been made in Chapter I.
- Can be made in a 371 application even if one had not been made during Chapter I or Chapter II.

Lack of unity of invention before IPEA (Article 34(3)(a) and Rule 68)

- 1. Unity of invention is based on the same criteria as for the international search. (Article 17 and Rule 40).
- The IPEA may again <u>or anow</u> hold lack of unity of invention among those inventions searched, and invite the applicant to restrict the claims or pay additional examination fees.
- 3. Applicant can select the invention to be examined as the "main invention" (it does not have to be the first claimed invention) as well as those inventions for which additional fees are paid for examination.

Lack of unity of invention before IPEA (Article 34(3)(a) and Rule 68) (con't)

- 4. If the applicant fails to make an election, the first mentioned invention will be examined as indicated by the examiner on form IPEA/405.
- 5. Payment of additional examination fees may be made under protest.
- 6. Decision on a protest is made in same manner as in Chapter I.

- 1. PCT Rules 13.1-13.4, MPEP Appendix T.
- 2. PCT Administrative Instructions, Annex B, Parts Land II (examples), MPEP Appendix AI.
- 3. 37 CFR 1.475, MPEP Appendix R, MPEP 1850

Requirement of unity of invention (Rule 13)

1. An international application must relate to one invention only or,

"if there is more than one invention, the inclusion of those inventions is only permitted if all inventions are so linked as to form a single general inventive concept." (Rule 13.1).

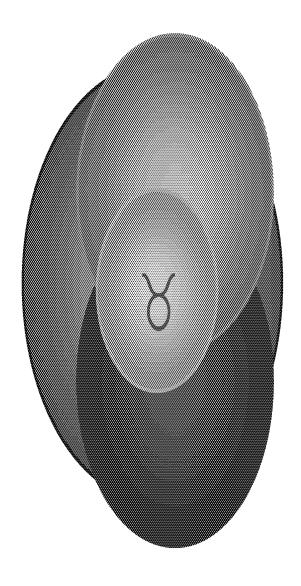
2. Unity of invention exists only when there is a technical relationship involving one or more of the same or corresponding "special technical features."

The expression "special technical features" means those technical features that define a contribution that <u>each</u> of the inventions, considered as a whole, make over the prior art. (Rule 13.2).

(For further explanation and examples concerning Unity of Invention, see Annex B, Administrative Instructions under the PCT)

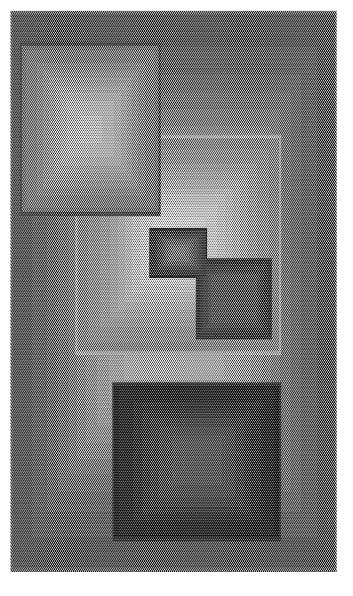
Multiple Claim Practice

EPO



Central Claiming

US



Peripheral Claiming

Clains in the same category

Some claims are drawn to product A and other claims are drawn to a completely different product B.

Unity of invention is lacking because no common special technical feature exists between the products.

Particular situations relating to unity of invention (Annex B of the PCT Administrative Instructions)

Copies included in appendices of MPEP

- There are three particular situations for which the method for determining unity of invention contained in Rule 13.2 is explained in greater detail in Annex B:
 - (i) combinations of different categories of claims;
 - (ii) "Markush practice"; and
 - (iii) intermediate and final products.
- The principles set out in Annex B are interpretations of, and not exceptions to, the provisions of Rule 13.2.

Examples of combinations of different categories of claims that may satisfy the requirement of unity of invention

- An independent claim for a given product, and
 - an independent claim for a process specially adapted for the <u>manufacture</u> of said **product**, and
 - an independent claim for a use of said product.

Examples of combinations of different categories of claims that may satisfy the requirement of unity of invention

- 2. An independent claim for a given process, and
 - an independent claim for an apparatus or means specifically designed for carrying out said process

Examples of combinations of different categories of claims that may satisfy the requirement of unity of invention

- 3. An independent claim for a given product, and
 - an independent claim for a <u>process</u> specially adapted for the manufacture of said <u>product</u>, and
 - an independent claim for an <u>apparatus</u> or means specifically designed for carrying out said <u>process</u>.

Claims in Different Categories

Claim 1 is to product Z.

Claim 2 is to a method of making product Z.

Claim 3 is to a method of using product Z.

Product Z links the inventions together as the <u>special</u> technical feature.

Therefore, unity exists

Lack of unity shown by <u>lack</u> of a special technical feature

In the example, if product Z was known in the art, the inventions would lack unity because product Z was not applicant's contribution over the prior art

Intermediate and final products (Rule 13.2 Part 1(g) of Annex B of the PCT Administrative Instructions)

The term "intermediate" means intermediate or starting products which have the ability to be used to produce final products through a physical or chemical change in which the intermediate loses its identity.

Intermediate and Final Products

Unity of invention may be present between intermediate and final products where the following two conditions are fulfilled:

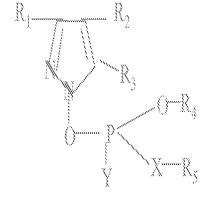
- (A) the intermediate and final products have the <u>same essential</u> <u>structural element</u>, in that:
 - (1) the basic chemical structures of the intermediate(s) and the final product(s) are the same, or
 - (2) the chemical structures of the two products are technically closely interrelated, the intermediate incorporating an <u>essential structural element</u> into the final product, and
- (B) the intermediate and final products are technically interrelated, this meaning that the final product is manufactured directly from the intermediate or is separated from it by a small number of intermediates all containing the same essential structural element.

Internediate/Final Products

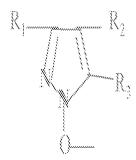
Example 25

Claim 1: R

Claim 2:



The chemical structure of the intermediate and final product are technically closely interrelated. The essential structural element, a "pyrazolo", incorporated into the final product is:



Therefore, unity exists between claims 1 and 2 if the ring structure makes a contribution over the prior art.

Example 26

Claim 1: (final product)

Claim 2: (intermediate)

Unity exists since the final product is made by a known ring closure reaction of the intermediate and the essential structural element is the linkage comprising the two phenyl rings and the triazole ring. The compounds are closely interrelated.

Markush Practice (Rule 13.2 Part 1(f) of Annex B of the PCT Administrative Instructions)

Markush practice: a single claim defines alternatives, chemical or non-chemical.

The requirement of a technical interrelationship and the same or corresponding <u>special technical features</u> as defined in Rule 13.2 are considered to be met when the alternatives are of a <u>similar nature</u>.

Markush Practice

When the Markush grouping is for alternatives of chemical compounds, they are regarded as being of a <u>similar nature</u> if the following criteria are fulfilled:

- (A) all alternatives have a common property or activity, and
- (B)(1) <u>a common structure</u> is present, i.e., a significant structural element is shared by all of the alternatives, or
- (B)(2) in cases where the common structure cannot be the unifying criteria, all alternatives belong to a recognized class of chemical compounds in the art to which the invention pertains.

Narkush Practice

Example 18 - common structure:

Claim 1: A compound of the formula:

wherein R^{\dagger} is selected from the group consisting of phenyl, pyridyl, thiazolyl, triazinyl, alkylthio, alkoxy and methyl; $R^2 - R^4$ are methyl, benzyl or phenyl.

The disclosure states that the compounds are useful as pharmaceuticals for the purpose of enhancing the capacity of the blood to absorb oxygen.

Narkush Practice

In this case the indolyl moiety is the <u>significant structural</u> element that is shared by all of the alternatives. Since all the claimed compounds are alleged to possess the same utility, unity may be present.

But since the indolyl structure is known, it does not make a contribution over the prior art, *therefore unity is lacking*

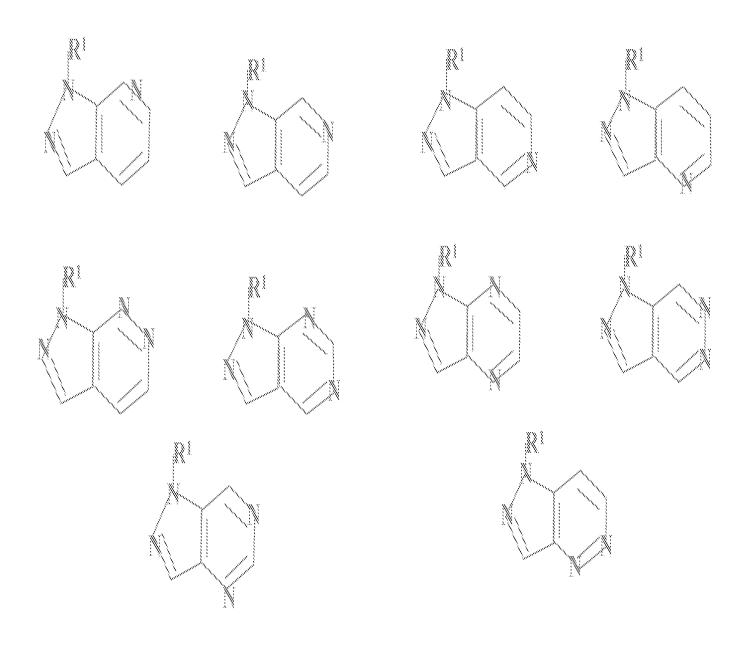
Example

Claim 1. Compounds of the formula

where one or two of W, X, Y and Z is Nitrogen and the rest are Carbon; \mathbb{R}^1 is H, Alkyl, Aryl, Heteroaryl....

How many different special technical features are found?

10 Different STF's



Example 22

Claim 1: A compound of the formula

(Polyhexamethyleneterephthalate)

100a/n a/50

Example 22 (con't)

Administrative Instructions Under the PCT

The compound obtained by esterifying the end COOH radical of known polyhexamethyleneterephthalate with CH2O has a thermal degradation resistant property, due to the reduced number of free COOH radicals which cause thermal degradation.

In contrast, the compound obtained by esterifying the end COOH radical of known polyhexamethyleneterephthalate with a vinyl compound containing a

CH₂=CH=\(\sum_\) CH₂O moiety serves as raw material for a setting resin when mixed with unsaturated monomers and cured (addition reaction).

All esters covered by the claim do not have a property or activity in common. For example, the product obtained through esterification with the " CH_2 = CH " vinyl compound does not have a thermal degradation resistant property.

Since there is no common property or activity, Unity of Invention is lacking.

Example

Claim: A compound of the formula:

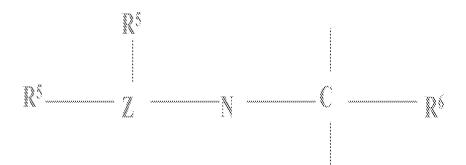
where R¹ is alkyl, alkenyl, alkynyl or Cy, where Cy stands for substituted or unsubstituted cycloalkyl, cycloheteroalkyl, aryl or heteroaryl;

X is a 1-5 carbon chain interrupted by or attached to one or more of the following groups: CO, COO, OCO, CONR³, NRCO, SO, SOO, NR³;

Example (con't)

Y is a 1-14 carbon chain which may be interrupted by or attached to one or more of the following groups; CO, COO, CONR³, NR³CO, SO, SOO, NR³.

where \mathbb{R}^3 is the same as \mathbb{R}^4 or is a structure of the formula:



Example (con't)

provided that:

when X is saturated and 1-4C, X must contain a heteroatom of O, N or S; or \mathbb{R}^2 must contain a methyl-indolyl-phenyl moiety; or \mathbb{R}^1 must contain a Cygroup.

Example (con't)

What is the main (or first) invention being claimed here?

The simplest structure formable is when

(Ethyl Ether)